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HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEWS

Sickle Hemoglobin (*Hb S*) Allele and Sickle Cell Disease: A HuGE Review

A. Ashley-Koch,[1] Q. Yang,[2] and R. S. Olney[2]

Sickle cell disease is caused by a variant of the β-globin gene called sickle hemoglobin (*Hb S*). Inherited autosomal recessively, either two copies of *Hb S* or one copy of *Hb S* plus another β-globin variant (such as *Hb C*) are required for disease expression. *Hb S* carriers are protected from malaria infection, and this protection probably led to the high frequency of *Hb S* in individuals of African and Mediterranean ancestry. Despite this advantage, individuals with sickle cell disease exhibit significant morbidity and mortality. Symptoms include chronic anemia, acute chest syndrome, stroke, splenic and renal dysfunction, pain crises, and susceptibility to bacterial infections. Pediatric mortality is primarily due to bacterial infection and stroke. In adults, specific causes of mortality are more varied, but individuals with more symptomatic disease may exhibit early mortality. Disease expression is variable and is modified by several factors, the most influential being genotype. Other factors include β-globin cluster haplotypes, α-globin gene number, and fetal hemoglobin expression. In recent years, newborn screening, better medical care, parent education, and penicillin prophylaxis have successfully reduced morbidity and mortality due to *Hb S*. *Am J Epidemiol* 2000;151:839–45.

anemia, sickle cell; epidemiology; genetics; *Hb S*; hemoglobin, sickle; public health; sickle cell trait

GENE

The β-globin gene is located on the short arm of chromosome 11. It is a member of the globin gene family, a group of genes involved in oxygen transport. Other members of this gene family include the α-, γ-, δ-, ε-, and ζ-globin genes. The globin genes are developmentally regulated, such that certain genes are expressed at specific times during human development. Two β-globin protein chains combine with two α-globin protein chains and a heme to form the predominant hemoglobin (Hb) found in human adults.

GENE VARIANTS

Over 475 β-globin gene variants exist, and several result in life-threatening illness (1). This review focuses only on the sickle hemoglobin (*Hb S*) variant and its relation to sickle cell disease. To that end, the MEDLINE literature search strategy used for this review was: sickle cell [all fields] AND epidemiology [all fields] AND English [language] AND 1988/05: 1999/08 [publication date]. Articles in which sickle cell disease was not the main focus were omitted. The articles chosen for inclusion were those that contained information pertinent to this review and were primarily population-based or cohort studies.

With respect to the *Hb S* variant, the molecular nature is a substitution of valine for glutamic acid at the sixth amino acid position in the β-globin gene. Individuals of African descent exhibit the highest frequency of at-risk genotypes associated with *Hb S*. However, individuals of Mediterranean, Caribbean,

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Abbreviations: AHCPR, Agency for Health Care Policy and Research; Hb, hemoglobin; *Hb A*, normal variant of the β-globin gene; *Hb S*, sickle variant of the β-globin gene; ICD-9, *International Classification of Diseases*, Ninth Revision.

[1] Office of Genetics and Disease Prevention, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA.
[2] Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA.
Reprint requests to Dr. Allison Ashley-Koch, Center for Human Genetics, Duke University Medical Center, Box 3445, 026 CARL Building, Durham, NC 27710.

South and Central American, Arab, and East Indian descent also exhibit high frequencies of at-risk genotypes (2). Table 1, showing data from a California newborn population (3), provides the birth prevalence of β-globin gene variants by ethnicity.

DISEASES

The term "sickle cell disease" refers to a collection of autosomal recessive genetic disorders characterized by the *Hb S* variant of the β-globin gene. More than 50,000 Americans are affected with sickle cell disease, making it one of the most prevalent genetic disorders in the United States (2). Individuals who are affected with sickle cell anemia have two copies of this variant (*Hb SS*), and the primary hemoglobin present in their red blood cells is sickle hemoglobin. Individuals affected with other types of sickle cell disease are compound heterozygotes. They possess one copy of the *Hb S* variant plus one copy of another β-globin gene variant, such as *Hb C* or Hb β-thalassemia. These individuals produce a mixture of variant hemoglobins. Carrier individuals have one copy of the sickle variant and one copy of the normal β-globin gene (*Hb AS*), producing a mixture of sickle hemoglobin and normal hemoglobin. The carrier state for sickle cell disease is often referred to as "sickle cell trait." Although individuals with sickle cell trait do not express sickle cell disease, one study found that sickle cell trait may be a risk factor for sudden death during physical training (4). In addition, individuals with sickle cell trait are protected from malaria infection (5). The high frequency of the *Hb S* variant is believed to be a result of this protective effect.

Morbidity

The hemoglobin of individuals with sickle cell disease polymerizes in red blood cells upon deoxygenation. This causes the red blood cells to change from the usual biconcave disc shape to an irregular sickled shape. In addition to the irregular shape, sickled red blood cells also have a propensity to adhere to the walls of blood vessels. Thus, sickled red blood cells can clog blood vessels, preventing normal blood flow and decreasing delivery of oxygen to organs and tissues. Sickled cells are also extremely susceptible to hemolysis, causing chronic anemia (2). Chronic anemia is generally moderate and not a major source of morbidity for individuals with sickle cell disease. However, the presence of a viral infection, such as *Parvovirus* infection, can lead to a temporary reduction in red blood cell production and cause more severe, life-threatening anemia (2). This is called an aplastic crisis.

Primarily, morbidity in sickle cell disease arises from vaso-occlusive events or tissue damage resulting from obstructed blood flow. Some of the more common symptoms include pain crises, acute chest syndrome, cerebrovascular accidents, and splenic and renal dysfunction (2). Pain crises are episodes of excruciating musculoskeletal pain (6), and acute chest syndrome is a life-threatening pneumonia-like illness (7). Cerebrovascular complications include transient ischemic attacks, ischemic strokes, and hemorrhagic strokes, sometimes associated with seizures. Splenic sequestration is a result of blood pooling, and in life-threatening instances it can be associated with severe anemia and hypovolemic shock. After early infancy, individuals with sickle cell disease become susceptible to bacterial infections due to functional asplenia and disordered humoral immunity.

Sickle cell disease is a major public health concern that has great impact on both individuals and society. Between 1989 and 1993, there were an average of 75,000 hospitalizations per year in the United States among individuals with sickle cell disease. In 1996

TABLE 1. Birth prevalence of β-globin gene variants in a California newborn population, by ethnicity, 1990–1996*

Ethnicity	Gene variant†					
	Hb SS	*Hb AS*	*Hb S*/β^{+}-thalassemia	*Hb SC*	*Hb SD*	*Hb SE*
Asian	0/207,551	1/1,336	0/207,551	0/207,551	0/207,551	0/207,551
Asian Indian	0/15,843	1/725	1/15,843	0/15,843	0/15,843	0/15,843
Black	1/700	1/14	1/4,056	1/1,297	1/63,885	1/63,885
Hispanic	1/45,622	1/183	1/729,953	1/364,976	1/1,459,900/6	1/1,459,900/6
Middle Eastern	0/21,677	1/360	0/21,677	0/21,677	0/21,677	0/21,677
Native American	1/16,529	1/176	0/16,529	0/16,529	0/16,529	0/16,529
White	1/158,127	1/625	1/553,447	0/1,106,895	1,106,895	1,106,895

* Source: Lorey et al. (3).

† Hb, hemoglobin; Hb S, sickle hemoglobin. Gene variants: *Hb SS*, sickle cell anemia (includes *Hb S*/β^{0}-thalassemia); *Hb AS*, sickle cell trait; *Hb SC*, sickle hemoglobin C disease; *Hb SD*, sickle hemoglobin D disease; *Hb SE*, sickle hemoglobin E disease.

dollars, these hospitalizations cost $475 million annually (8). The average length of stay per hospital visit was 6.1 days, and adults tended to have longer stays than children and adolescents (8).

Mortality

Sickle cell disease is also associated with significant mortality. Table 2 provides average annual age-

TABLE 2. State-specific average annual mortality rates (age-adjusted) for sickle cell disease per 1,000,000 individuals during 1979–1995*

State	Overall	Sex		Ethnicity	
		Male	Female	Black	Other
Alabama	5.5	6.3	4.7	22.2	<0.1
Alaska	0.5	0.2	0.9	14.3	—†
Arizona	0.8	0.9	0.6	27.1	<0.1
Arkansas	2.8	3.2	2.4	18.4	—
California	1.5	1.7	1.4	20.9	<0.1
Colorado	0.7	0.7	0.7	17.8	—
Connecticut	1.4	1.5	1.4	17.7	<0.1
Delaware	2.8	3.3	2.4	16.9	—
District of Columbia	14.6	15.2	14.1	23.2	—
Florida	3.5	3.8	3.2	24.7	0.1
Georgia	5.3	5.9	4.7	19.9	<0.1
Hawaii	0.3	0.2	0.3	7.7	0.1
Idaho	—	—	—	—	—
Illinois	2.6	2.9	2.4	17.6	0.1
Indiana	1.7	1.8	1.6	21.5	<0.1
Iowa	0.3	0.4	0.3	18.5	<0.1
Kansas	1.3	1.3	1.3	22.9	<0.1
Kentucky	1.3	1.3	1.2	17.7	<0.1
Louisiana	5.3	6.4	4.2	17.5	0.1
Maine	0.1	0.1	—	8.8	—
Maryland	2.7	3.0	2.5	10.9	<0.1
Massachusetts	0.7	0.6	0.7	13.0	0.1
Michigan	2.5	2.7	2.4	18.5	<0.1
Minnesota	0.3	0.4	0.3	17.7	<0.1
Mississippi	6.6	7.9	5.4	19.2	—
Missouri	2.1	2.6	1.7	19.4	0.1
Montana	—	—	—	—	—
Nebraska	0.4	0.4	0.4	10.7	<0.1
Nevada	1.3	1.7	1.0	20.0	0.1
New Hampshire	<0.1	0.1	—	9.0	—
New Jersey	2.4	2.4	2.4	17.9	0.1
New Mexico	0.4	0.4	0.5	18.6	0.1
New York	2.9	3.0	2.8	18.4	0.3
North Carolina	4.2	4.9	3.6	19.4	0.1
North Dakota	0.1	—	0.2	16.2	—
Ohio	1.9	2.2	1.7	17.6	0.1
Oklahoma	1.5	1.9	1.1	19.3	<0.1
Oregon	0.3	0.4	0.2	14.3	<0.1
Pennsylvania	1.8	1.9	1.7	19.0	0.1
Rhode Island	0.8	0.4	1.1	20.7	0.1
South Carolina	6.3	6.9	5.7	21.7	<0.1
South Dakota	0.2	0.2	0.2	65.8	—
Tennessee	3.3	3.6	3.0	20.5	0.1
Texas	2.1	2.2	2.0	17.8	<0.1
Utah	0.2	0.2	0.1	27.0	—
Vermont	—	—	—	—	—
Virginia	2.2	2.3	2.0	11.6	0.1
Washington	0.5	0.5	0.5	17.5	<0.1
West Virginia	0.7	1.0	0.5	23.0	—
Wisconsin	1.0	1.5	0.6	20.8	<0.1
Wyoming	0.6	0.5	0.8	76.0	0.2

* Source: National Center for Health Statistics (9).
† Either no information was available or no individuals with sickle cell disease were observed in that category.

adjusted mortality rates for 1979–1995, by US state. To generate table 2, we used data from Multiple-Cause Mortality Files compiled by the National Center for Health Statistics for the years 1979–1995 (9). Multiple-Cause Mortality Files include demographic and geographic information on the decedent, *International Classification of Diseases*, Ninth Revision (ICD-9) (10) codes for the underlying cause of death, and information on up to 20 conditions listed on the death certificate. The Multiple-Cause Mortality Files exist in two formats: entity axis and record axis. We selected all records that contained the ICD-9 code 282.6 (sickle cell disease) anywhere in the record axis portion (sickle cell-associated deaths). 1990 US census data (11), stratified by state, age, sex, and race, were used to create the standard populations for calculation of age-adjusted annual mortality rates per 1,000,000 US residents. Note that overall and sex-specific mortality rates depend on the proportion of the population comprising at-risk ethnicities (such as persons of African and Mediterranean ancestries).

In 1987, the highest mortality rate among children and adolescents (<20 years) was observed between 1 and 3 years of age, and most deaths in this group were due to infections and cerebrovascular accidents (12). However, in more recent years, mortality in this age group appears to have been declining, most likely as a result of newborn screening programs (early diagnosis), more comprehensive medical care, parent education, and penicillin prophylaxis for prevention of infection (13). Among adults (≥20 years) with sickle cell disease, the causes of mortality are more varied (14). However, early mortality may be observed in individuals with more symptomatic disease, such as those who exhibit fetal hemoglobin levels below the 75th percentile, hemoglobin values below the 10th percentile, elevated white blood cell counts (>15,100 cells/mm^3), renal insufficiency, acute chest syndrome, and seizures (14).

ASSOCIATIONS

Sickle cell disease is caused only by the *Hb S* allelic variant of the β-globin gene. All individuals who are homozygous or compound heterozygous for *Hb S* exhibit some clinical manifestations of sickle cell disease. Symptoms usually appear within the first 6 months of life, but there is considerable variability in the severity of the disorder (15).

Genotype is the most important risk factor for disease severity. Individuals with *Hb SS* (sickle cell anemia) are most severely affected, followed by individuals with *Hb S*/β^0-thalassemia. Individuals with *Hb SC* and *Hb S*/β^+-thalassemia tend to have a more benign course of the disease (15). However, individuals with *Hb SC* have increased risk for thromboembolic complications, retinopathy, and renal papillary necrosis when compared with individuals with *Hb SS* (16). Table 3 shows the US incidence of sickle cell complications by genotype, and table 4 shows median survival by genotype. Individuals with *Hb SS* and *Hb S*/β^0-thalassemia have higher rates of acute chest syndrome (7) and pain crises (6) than individuals with *Hb SC* and *Hb S*/β^+-thalassemia. Additionally, the rate of cerebrovascular complications is highest among individuals with the *Hb SS* genotype compared with the other three genotypes (17). With respect to survival, individuals with *Hb SS* have a median survival nearly 20 years lower than that of individuals with *Hb SC*, probably because of the differences in clinical severity observed in individuals with these two genotypes (14).

In addition to genotype, other factors associated with disease severity have been identified, such as haplotype of the β-globin gene cluster (18), α-globin gene complement (15, 19, 20), and levels of fetal hemoglobin (20). However, the ability to predict disease course from birth remains limited (20). Thus,

TABLE 3. Incidence of complications of sickle cell disease in the United States, by genotype

Complication	Gene variant*			
	Hb SS	*Hb SC*	*Hb S*/β^0-thalassemia	*Hb S*/β^+-thalassemia
Acute chest syndrome (per 100 patient-years)†	12.8	5.2	9.4	3.9
Cerebrovascular accidents (per 100 patient-years)‡	0.6	0.2	0.1	0.1
Pain crises (per patient-year)§	0.8	0.04	1.0	0.4

* *Hb SS*, sickle cell anemia; *Hb SC*, sickle hemoglobin C disease; *Hb S*, sickle hemoglobin.
† Source: Castro et al. (7).
‡ Source: Ohene-Frempong et al. (17).
§ Source: Platt et al. (6).

TABLE 4. Median survival of individuals of all ages with sickle cell disease in the United States, by sex and genotype, 1980s*

Sex and genotype†	Median survival (years)
Male, *Hb SS*	42
Female, *Hb SS*	48
Male, *Hb SC*	60
Female, *Hb SC*	68

* Source: Platt et al. (14).
† *Hb SS*, sickle cell anemia; *Hb SC*, sickle hemoglobin C disease.

there remains much to learn about factors associated with sickle cell disease severity.

INTERACTIONS

Malaria

It is believed that the unusually high frequency of sickle cell trait (*Hb AS*) in individuals of African and Mediterranean ancestries has been maintained because carriers of that trait have lower rates of mortality from malaria infection compared with noncarriers (*Hb AA*). The *Hb S* variant appears to decrease the risk of infection by the malaria parasite, *Plasmodium falciparum*. Although malaria is often fatal in individuals with *Hb SS*, the protection from infection appears to operate in a *Hb S* dose-dependent manner (5). That is, individuals with *Hb SS* have an even lower risk of infection than individuals with *Hb AS*.

β-globin cluster haplotypes

A cluster of several other globin genes is located on chromosome 11 near the β-globin gene. Thus, this region is referred to as the β-globin cluster region. DNA markers in the β-globin cluster region are highly variable. The combination of DNA markers observed on a particular chromosome form what is called a haplotype. While many haplotypes exist for the β-globin cluster region, only specific haplotypes are found on chromosomes that carry the *Hb S* variant (18). These haplotypes are named for the geographic regions of Africa and the Middle East where they predominate (18).

The β-globin cluster haplotypes are associated with differing clinical severities in sickle cell disease. This is probably due to variation in hemoglobin and fetal hemoglobin concentrations. Both hemoglobin and fetal hemoglobin levels vary with respect to haplotype (19) and are correlated with clinical expression of sickle cell disease (14, 20).

Among the three most common haplotypes in sickle cell disease, the Senegal haplotype is associated with the most benign form of sickle cell disease, followed by the Benin haplotype. The Central African Republic haplotype is associated with the most severe form of the disease (19). In Africa, as well as in the United States, sickle cell patients with the Central African Republic haplotype have a twofold increased risk of complications and early mortality when compared with sickle cell patients with other haplotypes (19).

α-thalassemia

Coinheritance of the α-globin gene variant, α-thalassemia, among individuals with sickle cell disease appears to be protective against some sickle cell complications, such as acute chest syndrome, anemia, and cerebrovascular accidents (15, 19). However, it increases susceptibility to other sickle cell complications, such as pain crises (15).

Fetal hemoglobin

Increased levels of fetal hemoglobin are associated with a less severe clinical course of sickle cell disease (20). Some individuals have a genetic predisposition to unusually high levels of fetal hemoglobin due to adult overexpression of γ-globin chains. However, this rare condition, hereditary persistence of fetal hemoglobin, is only found in one of every 188,000 individuals with sickle cell disease (3). Among the majority of individuals with sickle cell disease, who do not have hereditary persistence of fetal hemoglobin, the residual levels of fetal hemoglobin vary considerably. Approximately 40 percent of this variation is accounted for by the X-linked F-cell production locus, and the β-*S* cluster haplotypes account for an additional 14 percent of the variation (21). Some therapies for sickle cell disease, such as hydroxyurea, act by raising fetal hemoglobin levels in affected individuals.

LABORATORY TESTS

Table 5 displays the sensitivity, specificity, and cost of tests commonly used to detect sickle cell disease. These tests detect the β-globin gene product, hemoglobin. Hemoglobin tests are performed on blood samples, including umbilical cord blood and dried blood spots, which are collected at any time following birth. DNA testing for examination of the β-globin gene can also be performed. For DNA testing, samples may be collected prenatally (e.g., collection of amniocytes or chorionic villus samples) or postnatally.

TABLE 5. Sensitivity and specificity of tests used to detect sickle cell disease*

Method	Sensitivity (%)	Specificity (%)	Cost (dollars) per test
Cellulose acetate/citrate agar electrophoresis	93.1	99.9	0.15–0.25
Isoelectric focusing	100	100	0.35–0.50
High performance liquid chromatography	100	100	0.10–1.75

* Sources: Sickle Cell Disease Guideline Panel, Agency for Health Care Policy and Research (2), and Lorey et al. (22).

The Agency for Health Care Policy and Research (AHCPR) has recommended hemoglobin electrophoresis, isoelectric focusing, and high performance liquid chromatography as accurate methods for newborn screening (2). The AHCPR states that DNA analysis is also acceptable, but it is costlier than the other methods. Sodium metabisulfite preparations or solubility tests are not recommended as methods for newborn screening. The AHCPR has also recommended that all diagnostic laboratories participate in quality assurance and proficiency testing programs, regardless of the type of test they perform (2). Quality assurance evaluation of most state newborn screening programs is conducted by the Centers for Disease Control and Prevention.

Tests used in the United States may not be cost-effective for the diagnosis of sickle cell disease in developing countries. In Kenya, another method, peripheral blood film, has been demonstrated to be the most cost-effective method. The sensitivity and specificity of the peripheral blood film method are 76 percent and 99.7 percent, respectively (23).

POPULATION TESTING

In 1972, the 92nd US Congress passed the National Sickle Cell Anemia Control Act (24). This law initiated grant support for screening programs, and in 1975, the first statewide newborn screening program for sickle cell disease began in the United States (25). However, it was the late 1980s before most states were performing sickle cell or hemoglobinopathy newborn screening (2). A study carried out in 1986 demonstrated that oral administration of penicillin could significantly reduce morbidity and mortality in children with sickle cell disease (26). On the heels of this discovery, in 1987, the National Institutes of Health supported early diagnosis by newborn screening as being beneficial to infants with sickle cell disease (27). In 1993, the AHCPR concluded that newborn screening combined with comprehensive health care would significantly reduce morbidity and mortality rates among infants with sickle cell disease (2). The AHCPR further recommended that all infants be tested for sickle cell disease, regardless of race (universal screening). The agency stated that targeting high risk racial or ethnic groups would not identify all affected infants, because of the inability of health officials to reliably determine an infant's race by appearance, name, or self-report. In 1999, only four US states were not performing hemoglobinopathy screening: Montana, North Dakota, South Dakota, and Utah. The states of Maine, New Hampshire, West Virginia, Idaho, and Hawaii performed targeted screening. All other states performed universal screening (Harry Hannon and Barbara Adam, Centers for Disease Control and Prevention, personal communication, 1999).

In recent years, mortality due to sickle cell disease has decreased dramatically, primarily because of early diagnosis (via newborn screening), penicillin prophylaxis, better medical care, and education of family members. Today, most patients with sickle cell disease are living well into adulthood. Thus, future research will focus on providing these patients with a better quality of life through improved management of sickle cell-related symptoms, such as pain crises and stroke. More information on sickle cell disease can be found on the websites listed in table 6.

TABLE 6. Online resources pertaining to sickle cell disease

Resource	World Wide Web URL
General resources	
Ask NOAH about Sickle Cell Disease	http://www.noah.cuny.edu/genetic_diseases/sickle.html
March of Dimes	http://noah.cuny.edu/pregnancy/march_of_dimes/birth_defects/siklcell.html
National Heart, Lung, and Blood Institute	http://www.nhlbi.nih.gov/health/public/blood/index.htm
Genetics databases	
Human Gene Mutation Database	http://www.uwcm.ac.uk/uwcm/mg/search/119297.html
Online Mendelian Inheritance in Man (OMIM)	http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?141900
Educational resources	
Harvard University	http://www-rics.bwh.harvard.edu/sickle/scd.html
University of Chicago	http://uhs.bsd.uchicago.edu/uhs/topics/sickle.cell.html
National Heart, Lung, and Blood Institute	http://www.nhlbi.nih.gov/health/prof/blood/index.htm
Support groups	
Sickle Cell Disease Association of America	http://www.sicklecelldisease.org/
Sickle Cell Foundation of Georgia	http://www.mindspring.com/~sicklefg/
Sickle Cell Information Center	http://www.emory.edu/PEDS/SICKLE/

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